23. (Amended) The method of claim 22, wherein the composition comprises four human x bovine UK reassortant rotaviruses.

32. (Amended) The method of claim 22, wherein the method comprises multiple administrations of the composition.

REMARKS

Claims 1 through 33 have been examined in the present application. Applicants have amended claims 1-5, 7-16, 22, 23 and 32 to set forth the invention with greater particularity as described in greater detail below. All amendments are supported by the specification as filed and no new matter has been added. Applicants respectfully request reconsideration of the pending claims in light of the claim amendments above and the following remarks.

The Examiner has noted that Applicants have not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e), because the specification does not contain a specific reference to the prior application(s) in the first sentence or in an application data sheet (37 C.F.R. 1.78(a)(2) and (a)(5)). Applicants have amended the first page of the specification to insert the cross reference to related applications. In particular, this application is a national phase application under 35 U.S.C. 371 of International Patent Application PCT/US99/17036, filed July 27, 1999, which claims the benefit of U.S. Patent Application No. 60/094,425, filed July 28, 1998, the entire contents of each incorporated by reference in the present application. Applicants believe the present amendment is fully supported by the formal filing papers for the present application as reflected on the Official Filing Receipt and that the amendment to the specification overcomes the Examiner's objection.

The Examiner further believes that the present application does not contain an abstract of the disclosure on a separate sheet as required by 37 C.F.R. 1.72(b). Applicants note that the present application is a national phase of an international application and that the original filing in the United States Receiving Office contained an

abstract on a separate sheet as published in WO 00/06196. A copy of the title page of the International Publication is attached hereto. Also attached is a copy of the Abstract page filed with the United States Receiving Office July 27, 1999 and the confirmation receipt postcard confirming receipt of the abstract on a separate sheet. Applicants believe that an abstract was originally filed in the application and the requirement under 37 C.F.R. 1.72(b) has been met.

Rejections Under 35 U.S.C. § 112, Second Paragraph:

Claims 1 through 21 stand rejected under 35 U.S.C. § 112, second paragraph, the Examiner believing that the claims are indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In particular, the Examiner believes that claim 1 is unclear because it cannot be determined what is intended by a transient low level fever and that although a definition is provided for fever in adults and pediatric subjects, there is no indication of what is intended by "transient." Further, the Examiner has noted that at least a portion of the subjects given the vaccine developed fever. Also, the Examiner has noted that it is believed that this rejection similarly effects claims 2-21, and especially claims 7-16.

Although Applicants do not agree with the Examiner's summary of the claims or the basis for this rejection, and in order to further expedite prosecution of certain subject matter, claims 1-5, 7-16, 20 and 21 have been amended to set forth the present invention with greater particularity. In particular, claim 1 has been amended to recite that the composition can be administered "without causing a transient low level fever in a statistically significant number of vaccinees." Therefore, while a certain individual that might receive the composition could develop a transient low level fever associated with the vaccine composition, that total number of individuals will not comprise a significantly significant number within the population of individuals to whom the composition is administered.

Regarding the term "transient," it is well known in the rotavirus vaccine art that certain vaccine compositions induce a low level fever that lasts a day or two

during the first week after administration of a composition. See, for example, Bernstein *et al.*, *Lancet* 354:287-290 (1999) cited by the Examiner and the references cited and incorporated by reference in their entirety at page 3, lines 17-24, including Bernstein *et al.*, *JAMA* 273:1191-1196 (1995); Flores *et al.*, *Lancet* 336:330-334 (1995); Perez-Schael *et al.*, *J. Clin. Microbiol.* 28:553-558 (1990); Flores *et al.*, *J. Clin. Microbiol.* 31:2439-2445 (1993); Halsey *et al.*, *J. Infect Dis.* 158:1261-1267 (1988); Taniguichi *et al.*, *J. Clin. Microbiol.* 29:483-487 (1991); Simasathien *et al.*, *Pediatr. Infect. Dis. J.* 13:590-596 (1994); Madore *et al.*, *J. Infect. Dis.* 166:235-243 (1992); and Joensuu *et al.*, *Lancet* 350:1205-1209 (1997). Applicants believe that the term "transient" is used in a manner consistent with that which is well known in the rotavirus art and which is consistent with the dictionary definition of the term. Therefore, Applicants do not believe the term "transient" to be indefinite.

The Examiner has alleged that claim 2 is vague and indefinite because the Examiner is apparently uncertain which of the contributed VP7 serotypes is from a parent human rotavirus and whether the parent reassortant virus is a non-reassortant rotavirus. Claim 3 has been alleged to be vague and indefinite because the Examiner is apparently unable to discern which parent virus serotype is contributing the VP7 antigen. Claim 5 is alleged to provide insufficient antecedent basis for the limitation "bovine x bovine" in line 1. Claims 5 and 15 recite the bovine rotavirus strain "KC-1" which the Examiner believes to be unclear. Claim 16 stands rejected because the Examiner does not believe there is sufficient antecedent basis for the limitation "parent rotavirus." Claims 20 and 21 are believed to be vague and indefinite because the Examiner is apparently unable to determine whether each reassortant is present in the composition at 10^3 - 10^5 plaque forming units or if the entire composition of reassortants comprise 10^3 - 10^5 plaque forming units. Finally, claim 28 is believed to be unclear because the composition from the claim it depends comprises all four rotaviruses in the same mixture, but claim 28 states that each reassortant is administered individually and the Examiner questions

whether each of the administrations comprise 10^5 - 10^6 plaque forming units or whether that is the total amount of rotavirus administered.

Although Applicants do not agree with the Examiner's interpretation of the claims, and in order to further expedite prosecution of certain subject matter, claims 1-5, 7-16, 20-23 and 32 have been amended to set forth the invention with greater particularity. Specifically, Claim 1 has been amended to recite a multivalent immunogenic composition comprising at least four bovine strain reassortant rotaviruses and a physiologically acceptable carrier, wherein each bovine reassortant comprises a single gene which encodes a protein immunologically cross-reactive with an antigenically distinct human VP7 serotype and the remaining 10 genes derived from the bovine UK strain. This amendment finds support in the specification at, for example, page 5, line 31 through page 6, line 26, and page 9, lines 3 through 29. Claims 2, 3, 7-13, and 16 have been amended to clarify that each of the at least four VP7 serotypes are selected from and derived from a human rotavirus of the recited sources. The rotavirus contributing the VP7 gene can be either a human rotavirus or can be a human x animal reassortant rotavirus comprising a human VP7 gene.

Claim 5 and Claim 1 have been amended to clarify that the antigen encoded by the VP7 gene is immunologically cross-reactive with a human VP7 serotype. This includes a bovine gene that encodes a protein that is immunologically cross-reactive with human VP7 serotype 10. Support for this amendment can be found at, for example, page 9, lines 15-17. Therefore, the reassortant rotavirus can comprise a bovine x bovine reassortant rotavirus that provides an antigen that is immunologically cross-reactive with a human serotype 10 VP7 antigen. This can include any gene derived from any bovine rotavirus that is immunologically cross-reactive with human rotavirus VP7 serotype 10 including, but not limited to the bovine rotavirus strain KC-1.

Claims 5 and 15 have been amended to recite a bovine x bovine reassortant rotavirus comprising a human rotavirus VP7 serotype 10 antigen immunologically cross-reactive from the bovine rotavirus strain KC-1 as deposited with

the American Type Culture Collection and designated ATCC VR-2615. Although Applicants believe that the rotavirus strain designation KC-1 is definitive this amendment has been made to further expedite prosecution. The amendments to claims 5 and 15 do not limit the claims in any way, but only clarify the term "KC-1" as would be recognized in the rotavirus art.

Claim 16 has been amended to set forth the invention with greater particularity. In particular, the term "parent" objected to by the Examiner has been removed from the claim. Further, the claim is properly dependent from claim 7, as Claim 7 is directed to the composition of claim 1, which is a quadrivalent immunogenic composition comprising human x bovine reassortant rotavirus of human VP7 serotype 1, human VP7 serotype 2, human VP7 serotype 3, and human VP7 serotype 4. Claim 16, as presented originally and as amended, further limits the composition to comprise the human x bovine reassortant rotaviruses wherein the human rotavirus VP7 serotype 1 gene is derived from human rotavirus strain D, the human rotavirus VP7 serotype 2 gene is derived from human rotavirus strain DS-1, the human rotavirus VP7 serotype 3 gene is derived from human rotavirus strain P, and the human rotavirus VP7 serotype 4 gene is derived from human rotavirus strain ST3. The amendments to claim 16 are not believed to limit the claim in any way, but are only to clarify certain terms.

Claims 20 and 21 have been amended to clarify that the *each bovine reassortant* of claims 1 and 7 comprising the multivalent immunogenic composition, including the human x bovine reassortants and the bovine x bovine reassortants, are present in the composition within the recited ranges. This amendment is not believed to limit the scope of the claims in any way, but merely clarifies the elements present in the composition.

Applicants do not believe that Claim 28 is unclear, but sets forth the claimed invention with the particularity and definiteness required by 35 U.S.C. § 112, second paragraph. Claim 22 upon which claim 28 depends clearly sets forth that each of the bovine reassortants is present in the composition at a dosage of less than $10^{6.0}$ plaque

forming units. Claim 28 merely establishes that the human VP7 serotype rotaviruses are administered to an individual sequentially. The composition is therefore fully combined in the body of the individual administered each of the individual rotaviruses in the amounts specified. This embodiment of the invention is fully supported by the specification as filed. See, for example, page 10, lines 14-16.

Applicants believe that each of the Examiner's rejections under 35 U.S.C. § 112, second paragraph, has been addressed. Any amendments made to the claims is fully supported, as set forth above, and no new matter has been added. Further, each of the amendments to claims 1-5, 7-16, 20 and 21 do not limit the claimed invention in any way, but merely clarify certain terms as discussed in detail above. It is respectfully requested that the Examiner reconsider the rejection of claims 1-21 in light of the above amendments and remarks and withdraw all of the rejections under 35 U.S.C. § 112, second paragraph.

Rejections Under 35 U.S.C. § 112, First Paragraph:

Claims 1 through 21 stand rejected under 35 U.S.C. § 112, first paragraph, the Examiner believing the specification, while being enabling for eliciting an immunogenic response by administering the multivalent rotavirus vaccine, does not reasonably provide enablement for not causing a low grade fever upon administration of the composition. The Examiner therefore does not believe that the specification enables any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. In particular, it appears that the Examiner believes that a fever must not be caused in any individual to whom the claimed composition is administered. The Examiner has cited Bernstein *et al.*, (*Lancet* 354:287-290 (1999)) and Wandstradt *et al.*, (*Ann. Pharmacother.* 33:833-839 (1999)) to establish that it is unpredictable that administration of a multivalent rotavirus vaccine composition would not cause a fever. The Examiner further states that as the specification does not teach how the skilled artisan could administer the vaccine without

this most common side effect, an undue amount of experimentation would be required of the skilled artisan to use the invention in its full scope.

Applicants do not believe that the Examiner has properly interpreted the claimed invention or the specification. In order to clarify the present invention and to further expedite prosecution of this application, Applicants have amended claims 1 and 22 to recite "without causing a transient low level fever in a statistically significant number of vaccinees." This amendment is believed to be consistent with the teaching of the specification and to be fully enabled. Support for this amendment can be found, for example, at page 34, lines 27-30, page 37, lines 4-9, and Tables 5 and 6. Further, the data from the Finnish study disclosed in the specification was described as having an "essentially total lack of a febrile response to the human x bovine reassortant composition. (See the specification at page 35, lines 4-6). These data and the teachings of the specification fully enable the skilled artisan to be able to formulate and to administer the claimed compositions in the methods claimed without undue experimentation.

Claims 5 and 15 stand rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which the Examiner does not believe was described in the specification in such a way as to reasonably convey to one skilled in the art that the inventor(s), at the time the application was filed, had possession of the claimed invention. In particular, the Examiner does not believe that the specification teaches what the acronym KC-1 stands for. The Examiner apparently does not believe the term "KC-1" is commonly used in the art citing Brussow *et al.*, (*J. Gen. Virol.* 71:2625-2630 (1990) abst. only) as disclosing certain bovine rotavirus strains immunologically cross-reactive with human VP7 serotype 10, but not disclosing the bovine strain KC-1. Applicants note that a human x bovine rotavirus reassortant comprising a VP7 gene which encodes a protein immunologically cross-reactive with the human VP7 serotype was deposited with the American Type Culture Collection, June 4, 1998 under the conditions of the Budapest Treaty and designated ATCC VR-2615. Applicants have amended claims 5 and 15 to insert the ATCC designation for a bovine antigen immunologically cross-reactive with

the human rotavirus VP7 serotype. This amendment is not believed to limit claims 5 and 15 in any way, but merely clarifies the term "KC-1."

Applicants believe that all of the Examiner's rejections under 35 U.S.C. §112, first paragraph, have been addressed and overcome. It is respectfully requested that the Examiner reconsider and withdraw all of the rejections on this basis in light of the above amendments and remarks.

Rejections Under 35 U.S.C. § 103(a):

Claims 1-4, 6-14, and 16-33 stand rejected under 35 U.S.C. § 103(a) as unpatentable over Hoshino *et al.* (*J. Med. Virol.* 51:319-325 (1997)) and Clarke *et al.* (US Patent 6,113,910). In particular, the Examiner has summarized the present invention as drawn to a multivalent immunogenic composition and method for sti[mulating an immune response] comprising at least four human x bovine strain reassortant rotavirus, where each rotavirus is an antigenically distinct human VP7 serotype which is administered at less than 10^6 plaque forming units. The VP7 gene is derived from human VP7 serotype 1, serotype 2, serotype 3, serotype 4, and the like with the remaining genes derived from a bovine rotavirus UK strain. The Examiner believes that Hoshino *et al.* teaches "multivalent immunogenic compositions" comprising a human VP7 gene derived from various human rotaviruses of defined VP7 serotypes. These reassortant rotaviruses were administered to guinea pigs as separate isolates. The Examiner reasons that if the four isolates had been combined and administered, the combination would have obviously been immunogenic. The reference is characterized by the Examiner as being silent with respect to the amount of plaque forming units administered to the guinea pigs, but then reasons that because Hoshino *et al.* used parent reassortant strains that contain identical lot numbers as those taught in the specification that the Hoshino *et al.* reference teaches immunogenic compositions comprising less than 10^6 plaques forming units of rotavirus reassortants.

Applicants traverse the present rejection and strongly disagree with the Examiner's interpretation of Hoshino *et al.* and the content of the present specification. In particular, Hoshino *et al.* discloses the construction of four *double* gene substitution

human x bovine rotavirus reassortants as vaccine candidates. The double gene substitutions comprise both a human VP7 serotype antigen and a human VP4 serotype antigen, therefore the reassortants taught by Hoshino *et al.* have two human rotavirus genes and the remaining 9 rotavirus genes from a bovine rotavirus source. Multivalent immunogenic compositions comprising reassortants of this type are not claimed in the present application. Further, while particular lots of certain human x bovine rotavirus reassortants that were disclosed in Hoshino *et al.* were also used in particular embodiments of the present invention, no conclusions or inferences can be made about either the immunogenicity of the compositions when used in particular amounts as disclosed and claimed in the present application or whether the compositions will or will not induce a transient febrile condition. In addition, the present specification does not define the particular lot numbers of human x bovine reassortant rotavirus as containing less than 10^6 plaque forming units, but that the reassortant rotavirus obtained from of the various virus lots can be adjusted to any appropriate concentration.

Further, it should be noted that the Examiner acknowledges that Hoshino *et al.* do not teach an immunogenic composition comprising all four reassortants, or compositions additionally comprising serotypes 5, 9 and/or bovine reassortant serotype 10. Further, Hoshino *et al.* do not disclose the use of citrate buffer, or various adjuvants, nor does the reference disclose the compositions in a lyophilized from, or the use of an administration schedule that requires each reassortant to be orally administered sequentially, combined, or multiple administrations of three doses. The Examiner has therefore cited Clark *et al.*, as teaching a rotavirus reassortant vaccine comprising multiple reassortants, where at least one gene segment encodes VP7 from human rotavirus serotypes 5, 8, 9, and 10, the use of various buffers and the preparation of the multivalent vaccine composition in liquid dose form, and also as a lyophilized composition and further comprising an adjuvant. The Examiner believes that one of ordinary skill in the art at the time the invention was made would have been motivated to combine the multiple reassortants of Hoshino *et al.* into a multivalent vaccine composition taught by Clark *et al.* in order to administer all of the reassortants at the

same [time-omitted?] in case the recipient is unable to attend subsequent administrations and to antigenically diversify each composition. Further, the Examiner believes that one of skill in the art would be further motivated to combine the compositions of Hoshino *et al.* and Clark *et al.* because the individual compositions of Hoshino *et al.* are highly immunogenic and comprise the most epidemiologically important VP7 and VP4 serotypes, which the vaccine composition of Clark *et al.* contain other clinically significant strains that are effective in preventing infection. Also, the Examiner believes that, although neither reference teaches the composition further comprising bovine serotype 10, it would have been obvious for one of ordinary skill in the art at the time the invention was made to incorporate bovine serotype 10 into the multivalent vaccine composition of Clark *et al.* because the strain has been found in human infections and that one of skill in the art would have been motivated to administer each of the reassortant rotaviruses sequentially to prevent any eventuality of overwhelming an immune system of a recipient that has an underdeveloped or suppressed immune system.

Applicants traverse this basis of rejection. As above, Hoshino *et al.* disclose reassortant rotaviruses comprising 2 genes from a human rotavirus and the remaining 9 genes from a bovine rotavirus. Further, the rotaviruses constructed were administered individually to guinea pigs. It is well known in the rotavirus art that results relating to immunogenicity obtained with any rotavirus composition in animals does not correlate with results that might be obtained in humans, particularly infants. Also, it is well known that one of ordinary skill in the art can draw no conclusions as to an amount of rotavirus that would be necessary to obtain an immune response in humans. Clark *et al.* disclose a number of human x bovine reassortant rotaviruses. The reassortant rotaviruses in particular are composed of genes from various human rotavirus strains and the remaining genes from the bovine rotavirus strain WC-3 and its derivatives. Further, none of the rotavirus compositions that induce an immunogenic response to a human VP7 serotype disclosed by Clark *et al.* appear to have been administered at an amount of less than 10^6 plaque forming units. See for example, column 13, line 60 and column 19, lines 43-46 were the reassortant rotaviruses were administered at a dose of $10^{7.3}$ pfu. Also,

Applicants strongly disagree that there is any disclosure or suggestion of administering the claimed compositions or any other rotavirus vaccine composition sequentially for the reason provided by the Examiner in either Hoshino *et al.* or Clark *et al.* Therefore, any combination of Hoshino *et al.* and Clark *et al.* are not believed to either disclose or suggest the present invention as claimed. Further, Applicants believe that the compositions and methods of the present invention are patentable because the reassortant compositions of the present invention were not only found to be important because they demonstrated a lack of a febrile response, but also produced a protective response at a 10- to 100-fold lower virus dose than had been used for previous bovine rotavirus and human x bovine rotavirus reassortant compositions. (See page 35, lines 10-16).

Applicants respectfully request the Examiner to reconsider and withdraw the rejection of claims 1-4, 6-14, and 16-33 under 35 U.S.C. § 103(a) as unpatentable over Hoshino *et al.* and Clark *et al.* in view of the amendments and remarks above.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested. If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 206-467-9600.

Respectfully submitted,

Dated: 30 July 2002

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE SPECIFICATION:

A primary strategy for rotavirus vaccine development has been based on a "Jennerian" approach, which takes advantage of the antigenic relatedness of human and animal rotaviruses and the diminished virulence of animal rotavirus strains in humans. Kapikian *et al.*, in Vaccines 88, Chanock *et al.*, eds., Cold Spring Harbor Laboratory Press, Cold Spring Harbor, New York, pp. 151-159 [(1987)] (1988). Several candidate live oral rotavirus vaccines have been developed using this approach, where an antigenically-related live virus derived from a nonhuman host is used as a vaccine for immunization against its human virus counterpart. Examples of animal rotaviruses that have been used to vaccinate humans include bovine rotavirus strain NCDV (RIT4237, Vesikari *et al.*, Lancet, 2:[870] 807-811 (1983)), bovine rotavirus strain WC3 (Clark *et al.*, Am. J. Dis. Child., 140:350-356 (1986)) and rhesus monkey rotavirus (RRV) strain MMU 18006 (U.S. Patent 4,571,385, Kapikian *et al.*, Vaccines85, eds., Lerner *et al.*, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, New York, pp. 357-367 (1985)).

Please delete the paragraph beginning at page 3, line 17 and insert the following:

The general experience with monovalent and quadrivalent human x rhesus rotavirus reassortant vaccines has been that a transient low-level febrile episode occurs in about one-third of young infants 3 to 4 days after vaccination. Bernstein et al., JAMA 273:1191-1196 (1995); Flores *et al.*, Lancet 336:330-334 (1995); Perez-Schael *et al.*, J. Clin. Microbiol. 28:553-558 (1990); Flores *et al.*, J. Clin. Microbiol. 31:2439-2445 [(1993)] (1990); Halsey *et al.*, J. Infect Dis. 158:1261-1267 (1988); Taniguichi *et al.*, J. Clin. Microbiol. 29:483-487 (1991); Simasathien *et al.*, Pediatr. Infect. Dis. J. 13:590-596 (1994); Madore *et al.*, J. Infect. Dis. 166:235-243 (1992); and Joensuu *et al.*, Lancet 350:1205-1209 (1997).

Please delete the paragraph beginning at page 3, line 25, and insert the following:

Results of studies in humans with bovine rotavirus strains NCDV and WC3 (VP7 serotype 6) indicate that these particular bovine rotavirus strains do not appear to cause fever or other reactions. It should be noted that serotype 6 VP7 is not known to be present on human rotaviruses that are important in human rotavirus disease. Also, a bovine rotavirus was not found to be as immunogenic as the rhesus rotavirus when administered to humans. The bovine rotavirus strain NCDV (RIT4237 vaccine) has been evaluated in more than five efficacy trials in infants and young children. In these trials, the bovine RIT4237 vaccine was administered at a dose range of $10^{7.8}$ to $10^{8.3}$ tissue culture infectious doses $_{50}$ ($TCID_{50}$), with the usual dosage exceeding $10^{8.0}$ $TCID_{50}$. Also, in a dose-response study, Vesikari et al., Ped. Infect. Dis., 4:622-625 [(1995)] (1985)) observed that 15% (2/13) of four- to six- month old infants developed a homotypic antibody response when the vaccine was administered at a dose of $10^{6.3}$ $TCID_{50}$; 71% (10/14) when administered at a dose of $10^{7.2}$ $TCID_{50}$, and 100% when administered at a dose of $10^{8.3}$ $TCID_{50}$. Thus, the dose for this bovine rotavirus strain that produced an optimal immunogenicity was determined to be in the range of $10^{8.0}$ $TCID_{50}$.

At page 13, please delete the paragraph beginning at line 15, and insert the following:

Human x bovine reassortant rotavirus strains representing VP7 serotypes 1, 2, 3 and 4 were derived from the bovine UK Compton (UK) strain and from human rotavirus strains D (VP7 serotype 1, ATCC VR-970), DS-1 (VP7 serotype 2; Wyatt *et al.*, Perspect. Virol. 10:121-145 (1978)) and P (VP7 serotype 3; Wyatt *et al.*, Science 207:189-171 [(1983)] (1980)), and ST3 (VP7 serotype 4; Banatvala *et al.*, J. Am. Vet. Med. Assoc. 173:527-530 (1978)). Human rotavirus strains D, DS-1, and P were recovered from stools of children hospitalized with diarrhea; Strains D and DS-1 were propagated and passaged in gnotobiotic calves (Wyatt et al., 1978, supra; and Midthun et al., 1985, J. Virol. 53:949-954) and later grown only in tissue culture, while strain P was

grown only in AGMK tissue culture. Human rotavirus strain ST3 was isolated from a stool of an asymptomatic neonate and passaged in AGMK cells. The bovine UK Compton rotavirus strain was isolated in primary calf kidney cells from the stool of a colostrum-deprived calf with diarrhea. (Woode *et al.*, Res. Vet. Sci. 16:102-105 (1974)). The further passage of this virus in primary calf kidney cells was carried out by Flewett et al., at the Regional Virus Laboratory, East Birmingham Hospital, Birmingham, England and sent to the National Institutes of Health, Bethesda, MD. At the NIH the virus was serially passaged in primary bovine embryonic kidney cells, primary AGMK cells, and in diploid simian DBS-FRhL cells. The seed pool contained virus that was plaque purified in AGMK cells and passaged in primary calf kidney cell culture.

IN THE CLAIMS:

Please amend the claims as set forth in detail herein below. An Appendix showing all changes to the claims is attached to this amendment as required by 37 C.F.R. § 1.121(c).

1. (Amended) A multivalent immunogenic composition comprising at least four [human x] bovine strain reassortant rotaviruses and a physiologically acceptable carrier, wherein each [human x] bovine reassortant rotavirus comprises [an antigenically distinct] a single human VP7 gene derived from an antigenically distinct serotype and the remaining 10 genes derived from the bovine UK strain, and wherein the composition induces an immunogenic response to each antigenically distinct human rotavirus VP7 serotype without causing a transient low level fever in a statistically significant number of vaccines when each of the rotavirus reassortant [components] serotype is administered at a dosage of less than $10^{6.0}$ plaque forming units.

2. (Amended) The composition of claim 1, wherein the VP7 serotype antigen of the [human x] bovine rotavirus reassortant is contributed by a [parent] human rotavirus.

3. (Amended) The composition of claim 2, wherein the [parent] human rotavirus is selected from the group consisting of a human rotavirus VP7 serotype 1, a human VP7 serotype 2, a human VP7 serotype 3, a human VP7 serotype 4, a human VP7 serotype 5, and a human VP7 serotype 9.

4. (Amended) The composition of claim 2, further comprising a [bovine rotavirus x] bovine rotavirus reassortant comprising a bovine gene encoding a protein with the immunogenic reactivity of a human rotavirus of VP7 serotype 10.

5. (Amended) The composition of claim [1] 4, wherein the bovine x bovine reassortant rotavirus comprises a human rotavirus VP7 serotype 10 reactive antigen from the bovine rotavirus strain KC-1 as deposited with the American Type Culture Collection and designated ATCC VR-2615.

Please cancel claim 6 without prejudice.

7. (Amended) The composition of claim 1 which is a quadrivalent immunogenic composition comprising human x bovine reassortant rotavirus of human VP7 serotype 1, human VP7 serotype 2, human VP7 serotype 3, and human VP7 serotype 4.

8. (Amended) The composition of claim 1 which is a multivalent composition comprising human x bovine reassortant rotavirus of human VP7 serotype 1, human VP7 serotype 2, human VP7 serotype 3, human VP7 serotype 4, and human VP7 serotype 5.

9. (Amended) The composition of claim 1 which is a multivalent composition comprising human x bovine reassortant rotavirus of human VP7 serotype 1, human VP7 serotype 2, human VP7 serotype 3, human VP7 serotype 4, and human VP7 serotype 9.

10. (Amended) The composition of claim 1 which is a multivalent composition comprising human x bovine reassortant rotavirus of human VP7 serotype 1, human VP7 serotype 2, human VP7 serotype 3, human VP7 serotype 4, human VP7 serotype 5, and human VP4 serotype 1A.

11. (Amended) The composition of claim 1 which is a multivalent composition comprising human x bovine reassortant rotavirus of human VP7 serotype 1, human VP7 serotype 2, human VP7 serotype 3, human VP7 serotype 4, human VP7 serotype 9, and human VP4 serotype 1A.

12. (Amended) The composition of claim 1 which is a multivalent composition comprising human x bovine reassortant rotavirus of human VP7 serotype 1, human VP7 serotype 2, human VP7 serotype 3, human VP7 serotype 4, human VP7 serotype 5, and human VP7 serotype 9.

13. (Amended) The composition of claim 1 which is a multivalent composition comprising human x bovine reassortant rotavirus of human VP7 serotype 1, human VP7 serotype 2, human VP7 serotype 3, human VP7 serotype 4, human VP7 serotype 5, human VP7 serotype 9, and human VP4 serotype 1A.

14. (Amended) The composition of claim 7 further comprising a [bovine x] bovine reassortant rotavirus comprising a bovine gene encoding a protein with the immunogenically reactivity of a human rotavirus of VP7 serotype 10.

15. (Amended) The composition of claim 14, wherein the bovine x bovine reassortant rotavirus comprises a VP7 serotype 10 antigen from the bovine rotavirus strain KC-1.

16. (Amended) The composition of claim 7, wherein the [parent] human rotavirus VP7 serotype gene is derived from human rotavirus strain D (serotype 1), human rotavirus strain DS-1 (serotype 2), human rotavirus strain P (serotype 3) and human rotavirus strain ST3 (serotype 4).

20. (Amended) The composition of claim 7, wherein each [human x] bovine reassortant is formulated to provide a dosage of 10^3 to 10^5 plaque forming units.

21. (Amended) The composition of claim 7, wherein each [human x] bovine reassortant is formulated to provide a dosage of 10^5 to 10^6 plaque forming units.

22. (Amended) A method for stimulating the immune system to produce an immunogenic response to human rotavirus VP7 serotype antigen without significant transient low level fever in a statistically significant number of vaccinees,

which comprises administering a multivalent immunogenic composition comprising at least four VP7 serotypes of human rotavirus each administered at a dosage of less than $10^{6.0}$ plaque forming units and a physiologically acceptable carrier.

23. (Amended) The method of claim 22, wherein the composition comprises four human x bovine UK reassortant rotaviruses.

32. (Amended) The method of claim 22, wherein the method comprises multiple administrations of the composition.